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TITLE: A Randomized, Controlled Trial of Intranasal Oxytocin as an Adjunct to Behavioral Therapy for Autism Spectrum Disorder

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14. ABSTRACT
The primary objectives of this clinical study are test the hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions, and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD), and to examine whether neuroimaging measures of brain function and structure can predict CBT treatment response. To examine these questions, we will recruit and carefully characterize 150 men, ages 18-30, with ASD to participate in this study. Participants will be randomized to receive either social skills training or a stress management/relaxation therapy, and will be randomized to receive either intranasal oxytocin or placebo. Participants and evaluators will be blind to treatment condition. In year 1 of the study, we set up the study framework, including submitting applications for approval from the MGH and MIT Internal Review Boards, and the HRPO. We also received an IND from the FDA for the use of the oxytocin, trained study staff, and began setting up recruitment efforts. The study was approved by the HRPO in April 2014, and we initiated study procedures at this time. To-date, we have conducted baseline assessments with 12 participants, have completed neuroimaging with 10 participants, and have randomized 11 participants into treatment. There are no study findings to report at this time, as the study is ongoing.

15. SUBJECT TERMS
autism spectrum disorder, young adult, cognitive-behavioral therapy, social skills training, oxytocin, placebo-controlled, double-blind, clinical trial

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1. Introduction

The primary objectives of this clinical study are test the two hypotheses that (1) cognitive behavioral therapy (CBT) aimed at core social dysfunctions and (2) oxytocin (OT) administration prior to CBT sessions will each enhance social function in young adults with autism spectrum disorders (ASD). A third objective is to examine whether neuroimaging measures of brain function and structure can predict CBT treatment responsiveness. To examine these important research questions, we will recruit and carefully characterize 150 men, ages 18-30, with ASD to participate in this study. These will all be high-functioning patients with IQ scores in the average-to-above average range (90 and higher). We will randomly assign ASD volunteers into three 50-person groups, with stratification (equation) on age, ASD severity (ADOS score), and non-verbal IQ so that the three groups are equated on those important dimensions. The three groups are: (1) Group 1 (*All Placebo*), who will receive an active placebo behavioral treatment of 12 sessions of relaxation training, and placebo medication; (2) Group 2 (*CBT/placebo*), who will receive the experimental CBT 12-session treatment, and placebo medication; and (3) Group 3 (*CBT/OT*), who will receive the experimental treatment, and OT before 12 sessions of CBT treatment. Volunteers (patients) and evaluators will be blind to condition assignment (double-blind design). We will test the *hypothesis* that CBT helps ASD adults by statistically comparing Groups 1 and 2 on outcome measures (the inclusion of medication placebo equates expectancy effects across the two groups). We will test the *hypothesis* that OT enhances CBT effectiveness in ASD adults by statistically comparing Groups 2 and 3 on outcome measures. We will perform functional (fMRI) and structural (MRI) imaging with all participants prior to treatment, and will examine the relations between measures of brain function and structure with improvements on outcome measures.

2. Keywords:

autism spectrum disorder; young adult; male; cognitive-behavioral therapy; social skills training, stress management, oxytocin, placebo-controlled; double-blind; clinical trial

3. Overall Project Summary (As per Statement of Work)

Task 1. IRB approval
Submit clinical trial description documents to local IRBs and HRPO.
1a. Update consent forms to reflect local IRB and HRPO regulations (months 1) MIT+MGH
1b. Apply for MIT IRB approval (months 1-3) MIT

- **We initially submitted the application for IRB approval in May 2013, initial approval was given in October 2013.**
- **Approval for the continuing review at the MIT IRB was received on**

June 19th, 2014.

- **Approval for the continuing review at the MGH IRB was received on September 12, 2014.**

1c. Apply for MGH IRB approval (months 1-3) MGH
1d. Apply United States Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO) approval (months 2-5) MGH+MIT

- We received an IND from the FDA for the use of oxytocin in the study
- We submitted the protocol to the HRPO upon preliminary approval from MGH and MIT IRB and received approval from HRPO on April 4, 2014 for the MIT Site and on April 7th 2014 for the MGH Site.
- We created a CT.gov account for the study and have updated this account regularly, as per the CT.gov requirements.
- Both MIT and MGH received access to NDAR (National Database for Autism Research).

Task 2. Staff recruitment and preparation of testing materials, initial pilot study

This task involves setting up the system for subject recruitment, randomization and tracking. As well as setting up a system for continuously adding assessment results.

- **The study staff is as follows:**
  - **Aude Henin, Ph.D. (MGH PI)**
  - **Dina Hirshfeld-Becker, Ph.D. (independent evaluator at MGH)**
  - **Angela Utschig, Ph.D. (study therapist at MGH)**
  - **Jamie Micco, Ph.D. (study therapist at MGH)**
  - **Jennifer Park, Ph.D. (independent evaluator at MGH)**
  - **Christine Cooper-Vince, MA (study therapist at MGH)**
  - **Ben Shapiro, MA (study therapist at MGH)**
  - **Tim Soto, MA (study therapist at MGH)**
  - **Gagan Joshi, MD (study physician)**
  - **Janet Wozniak, MD (study physician)**
  - **Tanishia Choice, MD (study physician)**
  - **Satrajit Ghosh, Ph.D. (neuroimager and statistician, MIT)**
  - **Dorit Kliemann, Dr. (neuroimager and project coordinator, MIT)**
  - **Annie Cardinaux, Ph.D. (independent assessor at MIT)**
  - **Caitlin Malloy, Ph.D. (independent assessor at MIT)**
  - **Lexi Boudreaux, B.A. (research assistant)**
  - **Sophie Baron, B.A. (research assistant)**

- **We have trained study clinicians on the CBT therapy protocol, and the independent evaluators on the study measures**

- **We have initiated and continued regular meeting with MIT and MGH staff to jointly coordinate ongoing steps and topics.**

- **MIT and MGH staff have completed the work on developing a data entry system that will facilitate cross-site sharing of data**

2a. Prepare stimuli and scanner protocol (months 1-3) MIT
We will create a setup for stimulus presentation using the Psychophysics Toolbox for MATLAB. The setup will include stimulus presentation for functional localizers used in the imaging sessions as well as tests for attention during the pre and post periods. Prepare stimuli and presentation for RMET and Social cooperation task.

- **Sequences for functional and structural neuroimaging prior to treatment have been tested for study eligibility (all with whole-brain coverage in a higher resolution 32-channel coil):**
  - ***Resting State:*** **2x2x2 mm, TR=1.09s, TE=30 (2x- PA and AP phase encoding)**
  - ***Structural:*** **MEMPRAGE: 1x1x1mm, Multi-echo (with possible motion correction)**
  - ***T2 SPACE:*** **1x1x1mm, bandwidth matchedt o T1-weighted MEMPRAGE**
  - ***Diffusion weighted:*** **5mXXs, 2x2x2 mm, 61 directions, b=1000, 9 b=0 values (2x, PA, AP)**
  - ***Functional tasks:*** **3x3x3mm TR=2.5s, TE=30ms**

- These tasks have been successfully piloted and are functioning as expected.

2b. Setup software for behavioral testing (months 1-3) MGH+MIT
The research coordinator will install the study software on the study purchased laptops.

- We worked with developers of behavioral tasks to implement several behavioral tasks in the study.
- The behavioral tasks have been implemented as part of the assessment protocols and are working as expected.

2c. Run pilot experiments (months 5-7) MGH+MIT
Run the initial pilot study to ensure all components are operational.

- **The imaging protocol was piloted with several participants at MIT and is operating as expected.**

2d. Setup contract with pharmacy to supply drug and placebo after IRB approval.

- **We have been working with the MGH pharmacy, MGH mailroom, and the oxytocin distributor to obtain the oxytocin and placebo for the study. We successfully ordered and had shipped the oxytocin and placebo from the manufacturer, set up and implemented the blinding and randomization procedures with the MGH pharmacy, and have begun the administration of the drug/placebo.**

Task 3. Begin recruitment of 150 subjects (Specific Aim 1,2)
We will start recruiting subjects for the study in an ongoing basis, taking care to balance enrollment subject to characterization by clinical assessment.

3a. Announce study to clinics, referral sources (months 5-34) MGH

- **We created advertising materials including clinician and patient letters, advertisements to be posted on the subway and other public locations, and internet advertisements. We posted an ad on the local subway in July 2014 and reposted this ad in late October 2014. In addition, we have posted the ad on Craigslist, the MGH clinical trials website, and the MGH research website. We have also posted paper versions of the ad at local colleges and other public places.**

- **We have been meeting with local individuals and agencies (e.g., Lurie center, Child Psychiatry Department, and Bressler center) to inform them of our study and facilitate recruitment.**

- **We have developed, with the MGH pharmacy, a blocked randomization schedule that takes into account potential confounds such as level of autism severity, IQ, participant age, and current medication status.**

Task 4. Subject workflow (months 5-34)

After consenting, all subjects will undergo characterization by the clinician and if admitted to the study will be scheduled for imaging sessions and will be given directives on how to use the software.

4a. Telephone screen MGH

- **We developed the telephone screen and received MGH IRB Approval for its use.**
- **So far, we have received 29 calls from interested individuals and screened 19 participants**

4b. Characterization by clinician (Specific Aim 1) The characterization of subjects will include a formal clinical neurological examination and symptom assessment as described in Specific Aim 1, and a neuroimaging exam (Specific Aim 3). MGH + MIT

- The independent evaluators have been trained.

- To-date, we have consented and conducted baseline characterization with 12 participants and 10 of their parents. One of these participants was found ineligible at baseline. The remaining 11 participants were found to be eligible for the study and have continued with the study protocol.

4c. Schedule imaging session. MIT

- **We have conducted neuroimaging sessions with 10 participants.**

4d. Schedule CBT. MGH

-

Task 5. Perform neuroimaging, pre-treatment assessment and CBT(Specific Aim 2, 3; months 5-34) MGH + MIT

During this phase all subject data are collected. Each subject participates in the study for approximately 60 days.

5a. Collect imaging data during pre-treatment visit. MIT

Visit 1 (pre-treatment) consist of structural and functional brain measures requiring 1 hour in the scanner per visit. Diffusion, structural and functional data will be collected.

- **Neuroimaging sessions and pre-scanning ADOS-assessments are running smoothly.**

5b. Perform CBT for 12 weeks (12 sessions) MGH

- **We have randomized 11 subjects to treatment. Of the subjects currently in treatment, we expect to complete treatment and the week 12 (final) assessment with 3-4 participants over the next month.**

5c. Safety Review

Data collected for the proposed research will be stored in secure physical files, and password protected electronic files. All measures will be taken to protect the identity of participants. The files from this study may be available for review by USAMRAA, the Institutional Review Board (IRB) at MIT and MGH, and by representatives of other governmental agencies as part of their normal duties. All records will be kept in a confidential form. Otherwise, only the members of the research team conducting this study will have access to the study records. Information gained from this study may be used as part of a scientific publication, however, participants will in no way be personally identified. We will keep completely de-identified data wherever possible so that sharing of data is easiest and available for submission into the NDAR.

- **We have a DSMB meeting scheduled on 11/19/2014.**
- **Both MIT and MGH have received NDAR approval.**

Task 6. Analysis of data (Specific Aim 2,3; months 5-34) MIT + MGH
The data will be analyzed at both MIT and MGH. The focus at MIT will be on the analysis of the imaging data, while the focus at MGH will be to analyze the clinical assessment data.

- **Not yet initiated. We will begin preliminary data analysis within the next year.**

6a. Analysis of imaging data
The imaging data will be analyzed using the NiPyPE imaging analysis framework using tools from well established neuroimaging analysis packages (SPM, FSL and FreeSurfer).

- Analysis and quality assurance of individual imaging data have started. No group analyses have been initiated due to current limited sample size.

6b. Analysis of behavioral data
When each participant completes the study, the research coordinator will download the participants data from the secure web portal. Research coordinator will transcribe these data into the centralized study database for statistical analysis as described in the full research proposal.

- **Not yet initiated**

Task 7. Preparation and publication of results (Specific Aim 3,4; months 34-36)
Once sufficient data has been prediction models will be prepared in order to determine which form of treatment is most effective for a particular case characterization.

7a. Preparation of treatment prediction models MIT
7b. Preparation of manuscripts MIT+MGH
7c. Submission of curated data into NDAR.

- **Not yet initiated**

List of acronyms

DTI – Diffusion tensor imaging
fMRI – Functional magnetic resonance imaging
MGH – Massachusetts General Hospital
MIT - Massachusetts Institute of Technology
RCT – Randomized control trial

Problem Areas

We initially dealt with a 3-month delay in the project funding and project start

because of administrative issues as the primary project site was moved from MIT to MGH (Initial Project Start Date was October 1, 2012; funding not received until mid-December 2012 so actual start date is January 1, 2013). We also encountered several delays in the human subjects' approval process so that MGH/MIT IRB approval took nearly six months. There were additional delays in the approval process associated with the government shutdown in the fall of 2013, and we did not receive HRPO approval until April 2014. Because of these factors, had a significant delay in our ability to initiate study procedures. Since we have received IRB and HRPO approval, the study has gone smoothly. We have encountered no significant difficulties in recruiting, assessing, randomizing, and treating participants. We do not anticipate any significant problems with the study during the next reporting period.

4. Key Research Accomplishments

Nothing to Report

5. Conclusion

This study will address a critical clinical and public health need in a largely under-treated population at very high risk for disability at a critical point in development, the transition to adult life. It is increasingly recognized that young adults with autism spectrum disorders are at serious risk for a range of severe social, familial, functional, and economic problems. It is striking, however, that despite the great need of young adults with ASD for such treatment to enhance the quality of their lives, their relations with other people, and their opportunity for gainful employment, there is not yet any rigorous scientific evaluation of whether such CBT, which has been demonstrated to be so effective for so many other behavioral disorders, can help young adults with autism spectrum disorders. The proposed treatment, by focusing on enhancing social skills, adaptive behaviors, and resilience, will use well-established techniques in a novel way. In addition, its individualized nature will allow us to target the unique and complex needs of young adults with autism spectrum disorders. This study will be the first to (1) provide critical information about the efficacy of a novel CBT intervention in young adults; (2) provide evidence about whether oxytocin augmentation enhances CBT effectiveness; and (3) whether neuromarkers from neuroimaging can identify those young adults with autism spectrum disorders most likely to benefit from such treatments. We believe that this is an innovative and practical clinical trial that has great potential to lead to new forms of helpful support for young adults with autism spectrum disorders.

To achieve the overall goals of the study, during the next reporting period, we will achieve the following goals:

- conduct weekly staff meetings with various staff to review study progress, discuss clinical issues, and avoid rater/clinician drift
- continue study recruitment enrollment of study participants

- continue baseline assessment and neuroimaging protocols
- continue randomization to treatment and implement treatment protocols
- continue week 4, week 8, and week 12 assessment protocols
- continue imaging data analysis on a subject-by-subject level (individual imaging data).
- Initiate group analyses of baseline and neuroimaging data once sample size is sufficient

6. Publications, Abstracts, and Presentations
Nothing to Report

7. Inventions, Patents, and Licenses
Nothing to Report

8. Reportable Outcomes
Nothing to Report

9. Other Achievements
Nothing to Report

10. References
Nothing to Report

11. Appendices
Nothing to Report